REMARKS

Claims 1-3 and 11-28 were pending in this application when last examined. Claims 1-3 and 25-28 are currently amended and claims 11-20 have been cancelled. Claims 26-28 have been withdrawn.

Support for the amendments can be found in the specification and original claims as filed. Support can be found, for example, at page 8, lines 16-25, and lines 30-34, and at page 17, lines 19-24, of the specification. No new matter has been added.

ADVISORY NOTICE - INVENTORSHIP

At page 2, item 3, the Office Action indicates that no copies of the PCT/IB/306 forms were received in the August 25, 2009 Response to Denial of Request for Power of Attorney. Applicants respectfully disagree. Copies of these forms were in fact supplied with the Response - see, pages 4 and 5 of the August 25, 2009 Response.

As explained in the August 25, 2009 Response, the International Bureau deleted inventor Paul COHEN on January 28, 2005 and deleted inventor Gabriel PELTRE on April 11, 2005, via Form PCT/IB/306. Applicants again attach copies of the respective Form PCT/IB/306, in the Appendix. Accordingly, the inventive entity of the instant application is Daniel ZAGURY and Helene LE BUANNEC.

Applicants also submit in the Appendix the latest bibliographic data on file with the International Bureau for this International application PCT/FR2003/002733, which shows the only two remaining named inventors, Helene LE BUANNEC and Daniel ZAGURY.

Accordingly, it is again respectfully submitted that the previously filed Revocation and Power of Attorney, which was signed by the two correct inventors, be accepted, and that all future correspondence be directed to the practitioners associated with Customer Number 00466.

CLAIM REJECTION - 35 U.S.C. § 102

At page 3, item 7, the Office Action rejects claims 1-3 and 21-25 under 35 U.S.C. § 102(b) as being anticipated by ZAGURY et al. (WO 02/011759 A1; US 2004/0028647). Applicants respectfully traverse the rejection.

Currently amended claim 1 is directed to a stable immunogenic product for inducing antibodies raised against a TNFα protein. The product comprises immunogenic heterocomplexes comprising TNFα protein molecules associated with KLH carrier protein molecules, wherein more than 1% and less than 40% of the TNFα protein molecules are directly covalently linked to the KLH carrier protein molecules, and more than 60% of the TNFα protein molecules are non-covalently associated with the KLH carrier protein. ZAGURY fails to teach or suggest this product.

ZAGURY describes immunogenic compositions comprising a cytokinetic factor or other type of biological factor conjugated to a carrier protein, such as KLH (*see*, Abstract and paragraphs [0047]-[0049]).

In this regard, ZAGURY discloses the preparation of KLH-SIAB-VEGF immunogen, in Preparation 8, beginning at paragraph [0148], and KLH-SMCC-VEGF immunogen, in Preparation 9, beginning at paragraph [0162]. In both of these instances, ZAGURY prepares a compound having covalent linkages between factor VEGF, linkage molecule SIAB or SMCC, and carrier protein KLH. ZAGURY then completes the preparation by exclusion chromatography purification (*see*, [0158] and [0172]).

Further in this regard, ZAGURY discloses the preparation of KLH-Glutaraldehyde-VEGF immunogen in Preparation 10, and KLH-Glutaraldehyde-E7 immunogen in preparation 11. Again, ZAGURY completes these preparations by exclusion chromatography purification (*see*, paragraph [0180] and [0183]).

As a result of the preparation method and purification steps, the immunogenic compositions disclosed in ZAGURY comprise heterocomplexes of biological factor and KLH, wherein essentially 100 percent of the biological factor is covalently linked to the KLH carrier protein molecules. The exclusion chromatography step used in ZAGURY absolutely removes the unreacted VEGF or E7 proteins that are not covalently bound to KLH, leaving only the heterocomplexed protein. The ZAGURY preparation provides an

immunogenic composition wherein virtually 100% of the biological factor is covalently bound to the KLH carrier protein, but with zero biological factor molecules that are non-covalently associated with the KLH carrier protein.

In contrast to ZAGURY, the presently claimed immunogenic product comprises heterocomplexes of TNFα protein molecules associated with KLH carrier protein molecules, wherein less than 40% of the TNFα molecules are directly covalently linked to the KLH carrier protein molecules, and more than 60% of the TNFα protein molecules are non-covalently associated with the KLH carrier protein. This distinguishes over ZAGURY.

Applicants again refer to the ZAGURY Declaration originally submitted with the response filed June 18, 2009 for further support. The ZAGURY Declaration includes experimental evidence which shows that the presently claimed immunogenic product is distinguishable and falls outside the scope of the products produced according to the ZAGURY reference.

As detailed beginning at paragraph 32, and in Exhibit B, of the Declaration, two compounds were prepared (1) an immunogenic conjugate between TNFα and KLH prepared using the method disclosed by the ZAGURY reference, and (2) an immunogenic compound comprising TNFα and KLH prepared according to the method disclosed in Example 9 of the present application.

As explained in the Declaration, the ZAGURY compound (1) did not include a final size exclusion chromatography step.

In paragraph 44, the Declaration states that the reason why the final step of size exclusion chromatography was omitted is that this final step leads to a strong dilution of the final product which is detrimental to the performance of SDS PAGE electrophoresis used in the analysis. As further pointed out in the Declaration, however, the data shown in Exhibit B can still be interpreted, and shows that the ZAGURY compound falls outside the scope of the instantly claimed compound.

The Office Action completely discounts the Declarant's statements and the data in Exhibit B. As stated in the MPEP 716.01, "[E]vidence traversing rejections, when timely presented, must be considered by the examiner whenever present." Accordingly, the data presented in the Declaration, and in particular statements 32-57, must at least be considered by the Examiner.

Figure 3 of Exhibit B shows that by size exclusion chromatography, native KLH and human TNFα are clearly separated in two peaks - KLH peak at 58.47 min and TNFα peak at 83.75 min. The KLH-TNFα conjugate compound prepared according to ZAGURY shows a main peak at 57.23 min corresponding to the KLH-TNFα conjugate, and a secondary peak at about 83.75 corresponding to free TNFα molecules. The data in Figure 3 illustrates that the KLH-TNFα conjugate preparation of ZAGURY is essentially 100% covalently bound together with almost no free TNFα.

More importantly, the KLH-TNFα conjugate of ZAGURY is certainly outside the scope of "more than 60% of the TNFα protein molecules are non-covalently associated with the KLH carrier protein" as recited in instant claim 1. Even the "non-purified" (i.e., no size exclusion chromatography) KLH-TNFα conjugate comprises almost 100% covalently bound heterocomplex and the additional size exclusion chromatography step of ZAGURY would only serve to even further remove non-covalently bound TNFα and further purify the KLH-TNFα conjugate. (See, paragraphs 38 and 39 of Declaration).

It is further pointed out that the KLH-TNFα conjugate of ZAGURY prepared without a final size exclusion chromatography step can also be easily compared to the product of instant claim 14, which also does not include a size exclusion chromatography step. A comparison of the ZAGURY product to the presently claimed product is shown in Figure 4 of Exhibit B.

In Figure 4, a Western blot using anti-TNFα antibodies is shown. The immunogenic product according to instant claim 1 comprises several TNFα-containing chemical entities having a wide range of molecular weights (lane 2). These TNFα-containing entities comprise monomers of TNFα migrating to the bottom of the gel (approx. 20 kDa), as well as a series of entities of larger mass (greater than 75 kDa) up to and including the KLH-TNFα covalent conjugate migrating at the top of the gel.

As stated in the Declaration, at paragraphs 51-52, these numerous TNFα-containing chemical entities of intermediate molecular weight represent various TNFα oligomers. The presence of these entities also represent that these TNFα molecules were not covalently bound to KLH in the immunogenic product.

In contrast to the product shown in lane 2, the non-purified ZAGURY conjugate includes an amount of free TNFα monomer and KLH-TNFα covalently bound conjugate (lane 3). The free TNFα molecules that are present in the ZAGURY product of lane 3 are then removed by the final step of size exclusion chromatography. One would further recognize that an additional size exclusion chromatography step would remove the free TNFα and even further purify the KLH-TNFα conjugate.

The data set forth in the Declaration supports the fact that the KLH-TNFα conjugate disclosed in the ZAGURY reference does not include TNFα protein molecules associated with KLH carrier protein wherein 1-40% of the TNFα protein molecules are directly covalently linked to the KLH and more than 60% of the TNFα protein molecules are non-covalently associated with the KLH. Thus, the stable immunogenic product of instant claim 1 falls outside the scope of the teachings of the ZAGURY reference.

For all of these reasons, ZAGURY fails to teach or suggest, and fails to anticipate claims 1-3 and 21-25. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

PROVISIONAL OBVIOUS-TYPE DOUBLE PATENTING REJECTION

At page 9, item 9, the Office Action maintains a provisional nonstatutory double patenting rejection of claims 1-3 and 21-25 over claims 1-4, 6-8, 10-12, 14-17 and 19 of co-pending Application No. 11/735319. Applicants respectfully traverse the rejection.

First of all, this rejection is a provisional rejection as the co-pending application has not issued as a U.S. patent. Applicants request that this provisional rejection be held in abeyance until such time that claims are indicated as allowable in the instant application and the co-pending application issues as a U.S. patent.

Nevertheless in response to this rejection, present claim 1 is directed to a product comprising protein immunogenic heterocomplexes consisting of associations between TNFα protein and KLH carrier protein. Claims 2-3 and 21-25 depend from claim 1.

In contrast to the instant claims, claims 1-4, 6-8, 10-12, 14-17 and 19 of the '319 application are directed to a composition comprising inactivated TNFα or inactivated peptides of TNFα. As further developed in the dependent claims, the TNFα can be inactivated by subjecting the TNFα to chemical treatment such as with glutaraldehyde in the presence of carrier protein. The claims of the '319 application, however, fail to teach or

suggest an immunogenic product comprising protein heterocomplexes between TNFα protein and KLH carrier protein, and/or covalent linkages to the carrier protein. Chemical treatment can inactivate TNFα but does not require heterocomplex formation.

For at least this reason, claims 1-4, 6-8, 10-12, 14-17 and 19 of the '319 application do not teach or suggest, and would not have rendered obvious, claims 1-3 and 21-25. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

CONCLUSION

Entry of the above amendments is earnestly solicited. Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Should there be any matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized in this, concurrent, and future submissions, to charge any deficiency or credit any overpayment to Deposit Account No. 25-0120 for any

additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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APPENDIX:

The Appendix includes the following item(s):

☒ - PCT/IB/306 - PELTRE, Gabriel

☒ - PCT/IB/306 - COHEN, Paul

☒ - Latest bibliographic data on file with the International Bureau